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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,625	02/26/2004	Naoya Tsurushita	05882.0044.NPUS02	6526

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/788,625	TSURUSHITA ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *seq. comply*.

DETAILED ACTION

1. The preliminary amendment field 25 August 2004 has been entered in full.

Election/Restrictions

2. Applicant's election of the invention of Group VI, claims 30-33 in the reply filed on 08 May 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 30-33 are under examination.

Sequence Requirements

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. Figures 1(B) contains a sequence that is encompassed by the sequences rules and requires a sequence identifier (SEQ ID number). Applicant is required to either amend the Figures with the corresponding SEQ ID number or alternatively applicant may amend the Description of the Figures with the corresponding SEQ ID number. "It should be noted, though, that when a sequence is presented in a

drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP 2422.02. Applicants' cooperation is requested in reviewing the entire disclosure to ensure the present application is in sequence compliance.

6. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

7. APPLICANT IS GIVEN THE TIME ALLOTED IN THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Direct the response to the undersigned.

Specification

8. The disclosure is objected to because of the following informalities:

a. The Description of the Drawings is objected to because Figures 25 and 26 contain parts A-O and A-B, respectively that are not described in the Description of the Drawings. "For example, if the drawings show Figures 1A, 1B, and 1C and the brief

description of the drawings refers only to Figure 1, this is an error in the specification which must be corrected, rather than an application filed without all figures of drawings." See MPEP 601.01(g).

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention, i.e., "Methods for Producing Humanized Chicken Antibodies" or similar language that clearly reflects the claimed invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 30-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 30-33 are indefinite in the recitation of preparing expression vectors comprising a humanized heavy chain variable region or comprising a humanized light chain variable region in claim 30. Those of skill in the art recognize that heavy and light chain variable regions are contiguous sequences of four framework regions (FRs) and three complementarity-determining regions (CDRs) (i.e., FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4). Thus, one skilled in the art would not be reasonably apprised of what is contemplated by "expression vectors comprising DNA segments encoding a heavy

chain variable region of a humanized chicken immunoglobulin..." or "expression vectors comprising...DNA segments encoding a light chain variable region of the humanized chicken immunoglobulin...". Are the FR and CDR DNA segments on different/multiple vectors, are the variable regions fragments fused post-expression, do the expression vectors comprise DNA segments that encode different heavy chain variable regions, are the DNA segments one each vetcor a complete heavy or light chain variable region, or is some other meaning contemplated by the phrase? As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claims.

b. Claim 32 recites the limitation "the amino acid of the human acceptor immunoglobulin framework...". There is insufficient antecedent basis for this limitation in the claim. Base claim 30 recites two different human acceptor immunoglobulin framework regions (i.e., heavy and light) each of which comprises multiple framework amino acids. Thus, it is unclear which human acceptor immunoglobulin framework and more particularly, which amino acid of the human acceptor immunoglobulin framework is being referenced. See MPEP 2173.05(e).

c. Claim 33 is indefinite in the recitation "position selected from the group consisting of H67, H78, H93, L46, L66 and L67 of the human acceptor immunoglobulin framework". The phrase is relative in nature and there is no point of reference (i.e., sequence) and the amino acid residue positions H67, H78, H93, L46, L66 and L67 will have different meanings for different sequences. Further, are the residues numbered according to the Kabat numbering system or Chlothia numbering system for antibodies or residue 67 of a particular heavy chain amino acid sequence, or is some other

numbering system contemplated? Amending the claim to recite the SEQ ID numbers, thereby providing a point of reference would overcome this rejection.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andris-Widhopf et al (Journal of Immunological Methods, 242:159-181, 2000) and Queen et al (U.S. Patent 5,530,101, issued 6/25/1996, IDS reference A1 filed 1/10/05).

Claims 30-33 are being interpreted as drawn to a method of producing a humanized chicken immunoglobulin comprising preparing an expression vectors comprising DNA encoding heavy and light chain variable regions each comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing the transformed host cells to produce the humanized chicken immunoglobulin and wherein the humanized chicken immunoglobulin comprises framework residues from the chicken immunoglobulin that are capable of interacting with the CDRs and replacing rare amino acids in the human framework with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) and wherein a residue in at least one position selected from H67, H78, H93, L46, L66 and L69 of the human acceptor immunoglobulin framework is replaced.

Andris-Widhopf et al teach methods for the generation of chimeric chicken immunoglobulins and due to the ability to generate an immune response to highly conserved mammalian antigens that do not otherwise give rise to antibodies in mice and rabbits due to immunotolerance, chickens provide a useful source of clinically relevant antibodies that have human therapeutic potential and the use of single VH and VL genes in chicken immunoglobulins simplifies the use of genetic techniques for antibody engineering as only one set of oligonucleotide primers is needed for each

antibody chain (see entire document, particularly abstract, pp. 159-160, 169, 179 and Fig. 1). Andris-Widhopf et al do not specifically teach a method of producing a humanized chicken immunoglobulin comprising preparing expression vectors comprising DNA encoding heavy and light chain variable regions each comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing the transformed host cells to produce the humanized chicken immunoglobulin and wherein the humanized chicken immunoglobulin comprises framework residues from the chicken immunoglobulin that are capable of interacting with the CDRs and replacing rare amino acids in the human framework with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) and wherein a residue in at least one position selected from H67, H78, H93, L46, L66 and L69 of the human acceptor immunoglobulin framework is replaced. These deficiencies are made up for in the teachings of Queen et al.

Queen et al teach that while chimeric antibodies have proven somewhat successful in reducing the immunogenicity of nonhuman antibodies in human patients, a significant immunogenicity problem remains and Queen et al teach a method of producing humanized immunoglobulins that are less immunogenic in human patients and better suited for human therapy, said method comprising preparing expression vectors comprising DNA encoding a heavy and light chain variable regions each comprising CDRs from a nonhuman immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized immunoglobulin and wherein the humanized immunoglobulin

comprises framework residues from the nonhuman immunoglobulin that are capable of interacting with the CDRs and replacing rare amino acids in the human framework with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) as well as the replacement H67 and L46 in the human immunoglobulin frameworks (see entire document, particularly col. 1, 14-16 and Table 1 at col. 43).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method of making a humanized chicken immunoglobulin comprising preparing expression vectors comprising DNA encoding humanized heavy and light chain variable regions comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized chicken immunoglobulin, wherein the humanized chicken immunoglobulin further comprises framework residues from the chicken immunoglobulin that are capable of interacting with the CDRs, replacement of rare amino acids in the human frameworks with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) and replacement of human framework residue H67 or L46 in the humanized chicken immunoglobulin for therapeutic benefit in human patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a method of making a humanized chicken immunoglobulin comprising preparing expression vectors comprising DNA encoding humanized heavy and light chain variable

regions comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized chicken immunoglobulin, wherein the humanized chicken immunoglobulin further comprises framework residues from the chicken immunoglobulin that are capable of interacting with the CDRs, replacement of rare amino acids in the human frameworks with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) and replacement of human framework residue H67 or L46 in the humanized chicken immunoglobulin for therapeutic benefit in human patients in view of Andris-Widhopf et al and Queen et al because Andris-Widhopf et al teach methods for the generation of chimeric chicken immunoglobulins and due to the ability to generate an immune response to highly conserved mammalian antigens that do not otherwise give rise to antibodies in mice and rabbits due to immunotolerance, chickens provide a useful source of clinically relevant antibodies that have human therapeutic potential, however, a significant immunogenicity problem remains with chicken antibodies according to Queen and Queen et al teach a method of producing humanized immunoglobulins that are less immunogenic in human patients and better suited for human therapy compared nonhuman and chimeric antibodies, the method comprising preparing expression vectors comprising DNA encoding a heavy and light chain variable regions each comprising CDRs from a nonhuman immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized immunoglobulin and wherein the humanized immunoglobulin

comprises framework residues from the nonhuman immunoglobulin that are capable of interacting with the CDRs and replacing rare amino acids in the human framework with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) as well as the replacement H67 or L46 in the human immunoglobulin frameworks. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated and had a reasonable expectation of success to modify the chimeric chicken immunoglobulin of Andris-Widhopf et al and produce a humanized chicken immunoglobulin according to the method of Queen et al because chickens generate an immune response to highly conserved mammalian antigens that do not otherwise give rise to antibodies in mice and rabbits due to immunotolerance and thus, provide a useful source of clinically relevant antibodies that have human therapeutic potential and the use of single VH and VL genes in chicken immunoglobulins simplifies the use of genetic techniques for antibody engineering as only one set of oligonucleotide primers is needed for each antibody chain and humanized chicken immunoglobulins would overcome the immunogenicity problem that remains with chimeric antibodies. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a method of making a humanized chicken

immunoglobulin comprising preparing expression vectors comprising DNA encoding humanized heavy and light chain variable regions comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized chicken immunoglobulin, wherein the humanized chicken immunoglobulin further comprises framework residues from the chicken immunoglobulin that are capable of interacting with the CDRs, replacement of rare amino acids in the human frameworks with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) and replacement of human framework residue H67 or L46 in the humanized chicken immunoglobulin for therapeutic benefit in human patients in view of Andris-Widhopf et al and Queen et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. The art made of record and not relied upon is considered pertinent to applicant's disclosure.

Michael et al., U.S. Patent 6,143,559.

Tsurushita et al. Journal of Immunological Methods 295:9-19, 2004.

Nishibori et al. Biologicals 32 :213-218, 2004.

Nishibori et al. Molecular Immunology, 43 :634-642, 2006.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827